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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KERR, KATHLEEN M

ART UNIT PAPER NUMBER

1652

DATE MAILED: 09/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/091,244

Applicant(s)

GOKHALE ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) 1-18 and 22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 3/4/02, 7/30/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on January 29, 2004), Applicants filed a response and election received on July 1, 2004. Thus, Claims 1-22 are pending in the instant Office action.

Election

2. Applicant's election without traverse of Group III, Claims 19-21, in the reply filed on July 1, 2004 is acknowledged. Claims 1-18 and 22 are withdrawn from further consideration as non-elected inventions. Claims 19-21 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application Nos. 60/272,985 and 60/272,987 both filed on March 2, 2001 as requested in the declaration and the first lines of the specification. The instant application is also granted the benefit of priority for the U.S. non-Provisional Application No. 09/500,747 filed on February 9, 2000 and its provisional application 60/119,363 filed on February 9, 1999 as requested in the declaration and/or the first lines of the specification.

Declaration

4. The Examiner notes that the signed declaration filed on July 24, 2002 fails to check the box on the first page stating that this associated application was filed previously on March 4,

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2002 as 10/091,244. This is clearly a typographical omission and does not affect the validity of the declaration for the instant application. No action is required by Applicant.

Information Disclosure Statement

5. The information disclosure statements filed on March 4, 2002 and July 30, 2004 have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

Compliance with the Sequence Rules

6. By virtue of the filing of a sequence listing on October 22, 2002 as well as the amendments to the specification and Figure 3 citing SEQ ID NOs, the instant application now fully complies with the sequence rules.

Objections to the Specification

7. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Methods of Making Polyketides using Hybrid Polyketide Synthases---

8. The specification is objected to for lacking updated continuity data in the first paragraph. The instant application claims the benefit of U.S. non-Provisional Application No. 09/500,747 filed on February 9, 2000; however, the citation in the first paragraph must be updated to include the patent number USPN 6,753,173. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

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9. The specification is objected to for incomplete and/or unclear citations as follows:
- In paragraph [0015] and [0085], application 09/346,860 is noted and must be updated to USPN 6,221,641.
 - In paragraph [0085] reference to an attorney docket number must be updated to a clear reference, such as an application serial number or a patent number.
 - In the following paragraphs, "Tsuji *et al.* Biochemistry 2001" is disclosed without complete citation: paragraph [0097], [0131], [0143], [0145], and [0150].

Correction is required, particularly in view of Applicant's statement at the end of the specification to incorporate all references noted by reference in their entirety.

Objections to the Claims

10. Claims 19-21 are objected to for depending from non-elected claims. All the limitations of Claims 6, 4 and 1 must be incorporated into Claim 19.

11. Claims 19-21 are objected to for improper grammar in Claim 1. In line 6 of Claim 1, "chain from the a module" is improper; only one article should be used. The claim will be read as "a" since it is broader than ---the---. Correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 19-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The subject matter of the claims, namely, the PKS to be used, is wholly unclear in view of Claim 1. The terms "RAL" and "ERL" are unclear as to the nature of sequence they are. Figure 3 depicts these linkers RAL and N-ERL; however, little homology is

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shown and the starts and stops of these linkers are unclear. Moreover, no depiction of a C-ERL is shown; thus, its nature is wholly unclear.

From Claim 4, does the entire module need to be heterologous to other modules or can it simply have a domain substitution?

Additionally, the method steps of Claim 1 do not “prepare a desired polyketide synthase”; they merely assemble a PKS gene cluster. Thus, it is unclear how the method steps accomplish the claimed method to produce the PKS used in Claim 19.

The Examiner suggests utilizing language found in the product claims of parent USPN 6,753,173 with claims to the hybrid PKS, wherein said hybrid PKS would be used in the methods of the instant claims. If Applicant opts for identical product language to the allowed patent claims, filing of a terminal disclaimer for the methods of use of said product is suggested.

13. Claims 19-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The abbreviation “PKS” is unclear without definition in its first appearance in the claims. The Examiner suggests that that appearance read ---polyketide synthase (PKS)--- for clarity.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 19-21 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter

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which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to methods of making polyketides using PKSs having specific RAL and ERL linkers, which linkers lack adequate written description.

The Court of Appeals for the Federal Circuit has recently held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as be structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described (this is in contrast to the few examples of RAL and ERL linkers in the PKSs useable in the claimed methods), the same analysis applies wherein the product, used in the claimed methods, must have adequate written description. To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional

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characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, specific RALs and N-ERLs are depicted in Figure 3 from the erythromycin, rifamycin and rapamycin PKSs. The specification clearly indicates the use of not only these defined RALs and N-ERLs, but also variants thereof (see paragraph [0076] and [0082]). Describing the genus of RALs and ERLs must include adequate description of their structure and function, including variants. Since the RALs and ERLs are virtually devoid of structure, merely being found in a specific location (i.e., holding a position) in the PKS, a description of their structure, as a genus, is lacking in the specification. Functionally, RAL and ERL variants are described as being altered “in minor ways that do not affect the ability of the linker to ‘feed’ the nascent polyketide chain to the module in question” (see paragraph [0076]) thus being described by what they do rather than by what they are. This is not adequate written description of a product. For these reasons, the instant claims lack adequate written description of the claimed genus.

15. Claims 19-21 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using hybrid modular polyketide synthases, does not reasonably provide enablement for all hybrid polyketide synthases, such as aromatic PKSs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. To make all the hybrid PKSs for use in the claimed methods would require undue experimentation.

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The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification describes, almost exclusively, the use of modules of modular (Type I) PKSs in the hybrid PKSs disclosed. In fact, the RALs and ERLs of Claim 1 are only found in modular PKSs. No guidance is presented for producing hybrid PKSs that contain modules/domains from other types of PKSs. The nature of the invention is such that modular PKSs contain finite domains that correlate among all modular PKSs and, therefore, are exchangeable. The state of the prior art is that few type I/type II PKS hybrids are shown, and even fewer produce polyketides as required by the claimed methods. While the relative skill

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in the art for splicing genes together (and making hybrid proteins) is high, the predictability of making functional type I/type II PKS hybrids is low. For these reasons, the instant claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 19-21 are rejected under 35 U.S.C. § 102(b) as being anticipated by McDaniel *et al.* (see IDS 3/4/02, ref. #110). The instant claims are drawn to methods of making polyketide using hybrid PKSs having RAL and ERL linkers that facilitate nascent polyketide chain transfer.

McDaniel *et al.* teach KOS011-58 (see Figure 6) that encodes a hybrid PKS containing domains from DEBS and rapamycin PKSs. The natural DEBS RAL in between modules 1 and 2 is maintained. The N-ERL of DEBS module 3 is also maintained. Module 2 is heterologous to module 1 and 3 since, as a hybrid of DEBS and rapamycin domains, this hybrid module 2 is not naturally associated with either module 1 or module 3 of DEBS. McDaniel *et al.* also teach the production of compound 6 by this PKS construct (see Figure 6). DEBS modules 1 and 3 use methylmalonyl substrates, which are provided as evidenced by the production of polyketide.

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Conclusion

17. Claims 19-21 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Primary Examiner
Art Unit 1652

September 23, 2004